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**Review paper**

# Prophylaxis of hepatitis B virus (HBV) infection reactivation – recommendations of the Working Group for prevention of HBV reactivation

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## Abstract

Hepatitis B virus (HBV) is one of the main causes of chronic liver diseases and hepatocellular carcinoma. After infection the majority of HBV-infected patients achieve immune control leading to HBV-DNA stabilization at a low level. The risk of HBV reactivation rises significantly when HBV-infected patients receive immunosuppressive treatments. Presented recommendations provide guidelines for management of patients scheduled or undergoing therapies, which through their immunomodulatory activity contribute to the impairment of antiviral immunity, including chemotherapy, immunosuppressive treatment or biological therapy.

**Key words:** HBV, prevention, reactivation.

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## Introduction

Hepatitis B virus (HBV) is one of the main causes of chronic liver diseases and hepatocellular carcinoma. According to the World Health Organization (WHO), more than 260 million people worldwide are actively infected with HBV, and approximately 2 billion people may have been exposed to the virus. Most people with chronic or occult HBV infection are not aware that they are infected. For the above reasons, the risk of HBV reactivation rises significantly when HBV-infected patients receive immunosuppressive or anticancer treatments.

In the course of its replication cycle, HBV produces stable cccDNA minichromosome in infected hepatocytes, which serves as a matrix for the synthesis of viral DNA and proteins. It persists in the nuclei of infected cells for many years, and fails to respond to ongoing treatment [1]. The presence of cccDNA has been shown even after the loss of the HBs antigen and seroconversion to anti-HBs, which explains why the eradication of HBV infection is impossible. cccDNA serves as a matrix for reactivation even in patients with a distant history of hepatitis B.

Months to years after infection the majority of HBV-infected patients achieve immune control leading to HBV-DNA stabilization at a low level, decrease of inflammatory lesions in the liver, and even loss of HBsAg. The immune control of infection is based on three main mechanisms: 1) effective HBV-specific

CD4 and CD8 cell response, 2) antibody synthesis by B cells, and 3) innate immunity mechanisms. Humoral response involves primarily B cell-induced synthesis of antibodies, of which anti-HBs antibodies in the IgG class are of primary significance due to their HBV neutralization activity. The immune mechanisms in the course of HBV infection are sufficiently effective to bring about immune control, but insufficient to eliminate HBV from the body [2].

## Definition and phases of HBV reactivation

HBV reactivation is defined as a sudden at least 100-fold rise in the HBV-DNA level in patients with previously detectable HBV-DNA in response to immunosuppressive or anticancer therapy, or the detection of HBsAg or HBV-DNA in anti-HBc antibody-positive patients with previously negative test results for their presence.

It is clinically significant that HBV reactivation consists of three phases. In the first one, following the loss of immune control, HBV-DNA replication increases. The phase is asymptomatic on account of the non-cytopathic nature of HBV. Inflammatory reaction and hepatocyte necrosis manifested by an increased activity of alanine aminotransferase (ALT) as well as symptoms of hepatic dysfunction (hyperbilirubinaemia, coagulopathy, hyperammonaemia) develop in the second phase, usually after the effect of immunosuppression subsides, and immune system function is restored. In this phase, in addition to T cells, hepatocyte damage is attributable mainly to NK cells. In the third phase, unless hyperacute hepatitis develops, the inflammatory process resolves via the induction of processes attenuating excessive inflammatory reaction, and regeneration (recovery).

## Risk factors for reactivation of HBV infection

The risk of reactivation of HBV infection depends on multiple factors. It is higher (5 to 8 times) in HBsAg(+) patients compared to HBsAg(–) individuals, in patients with detectable HBV-DNA, and in patients who are negative for anti-HBs antibodies. Other risk factors include old age (> 65 years), male gender, underlying disease and, primarily, the type and duration of immunosuppressive treatment received by the patient [3, 4].

The reactivation of HBV infection is a particularly significant problem in patients undergoing therapies which through their immunomodulatory activity contribute to the impairment of antiviral immunity, including chemotherapy, immunosuppressive treatment (e.g. corticosteroids, cyclosporin, azathioprine) or biological therapy (e.g. monoclonal antibodies causing CD20 cell depletion, anti-tumor necrosis factor [TNF] antibodies).

In addition to virus- and host-dependent factors, the pathomechanism of HBV reactivation is conditioned primarily on the effects of applied biological treatment on the mechanisms of immune control of the infection. For example, the application of antibodies against the CD20 receptor (such as rituximab) causes the destruction of HBV-specific B cells and, as a consequence, a decrease in the number of circulating anti-HBV antibodies, including neutralizing antibodies targeted against the HBs antigen. Glucocorticosteroids have an inhibitory effect on the synthesis of antiviral cytokines and the proliferation of lymphocytes. Similarly, inhibitors of cytokines, chemokines and integrins disrupt the synthesis of anti-inflammatory cytokines by active lymphocytes and other cells of the immune system. Inhibitors of tyrosine kinases suppress the activation and proliferation of lymphocytes through their effect on intracellular signalling pathways. The pathomechanism of potential HBV reactivations has not been explained for all immunomodulatory drugs. For example, inhibition of the TNF-α pathway should not significantly affect the course of viral infections. On the other hand, multiple cases of HBV reactivation have been encountered with this treatment modality. It has been hypothesized that TNF-α may exhibit direct antiviral activity against cccDNA, similarly to interferon α, by affecting APOBEC family proteins [5].

## Epidemiology of reactivation of HBV infection

It is difficult to accurately estimate the reactivation rate of HBV infection because of varying definitions of reactivation, lack of adequate serological and virological monitoring, different durations of follow-up, and relatively small populations described in most publications. Another important aspect is that the prevalence of HBV infection varies depending on the region of the world. In view of these considerations the available data on the rate of reactivation of HBV infection are highly divergent. Nonetheless, patients with haematological diseases are believed to be a particularly susceptible population. A pooled analysis of 55 studies including a total of 3,640 HBsAg(–)/anti-HBc(+) patients receiving immunosuppressive therapy showed that the reactivation rate was 10.9% in patients with haematological diseases compared to 3.6% in patients with other disorders [6]. The risk of reactivation is

the highest in lymphoma patients: the reactivation rate without prophylaxis is 18-73% in HBsAg(+) patients, and 34-68% in HBsAg(–)/anti-HBc(+) patients [7-9]. High reactivation rates have also been reported in patients with acute leukaemias (HBsAg(+) patients: 61%, HBsAg(–)/anti-HBc(+) patients: 2.8-12.5%) and plasmocytoma (HBsAg(+) patients: 22%, HBsAg(–)/anti-HBc(+) patients: 6.8-8%) [7].

Treatment with B-cell depleting antibodies is associated with a high risk of reactivation regardless of the HBV status. The largest body of data has been accumulated for rituximab, an anti-CD20 monoclonal antibody which has been used in the treatment of B-cell lymphomas since 1997. At present, rituximab is used in a number of off-label indications in the treatment of autoimmune diseases (autoimmune cytopaenias, rheumatoid arthritis, systemic lupus erythematosus, psoriasis, glomerulonephritis), inflammatory conditions (Crohn's disease, multiple sclerosis), graft-versus-host disease, rejection of organ transplants, and post-transplant lymphoproliferative disease. In a metaanalysis of 15 studies involving a total of 1,312 HBsAg(–)/anti-HBc(+) patients with lymphomas treated with rituximab-based immunochemotherapy, the reactivation rate was 9% (range: 0-41%), with varying definitions of reactivation. The reactivation rate was higher in prospective (17%) than retrospective (7%) studies [10]. According to the authors, data from prospective studies reflect the actual risk better because of a more accurate definition of reactivation, closer monitoring, and longer follow-up period. Reactivation may occur at any time, both during and after the completion of immunochemotherapy, usually not earlier than after 2-3 cycles (median of 6 to 12 months after the last rituximab dose) up to approximately 2 years after the end of treatment [11]. The risk of reactivation associated with therapy based on the new anti-CD20 antibodies (obinutuzumab) is similar to that of rituximab.

In addition, a significant risk of reactivation is associated with the treatment of inflammatory and autoimmune diseases. Recent years have seen reports of reactivation of HBV infection in patients treated with proteasome inhibitors (e.g. bortezomib) and tyrosine kinase inhibitors: BCR-ABL (e.g. imatinib, dasatinib, nilotinib), JAK-1/2 (ruxolitinib), BTK (ibrutinib). An especially high risk of reactivation exists in patients after the transplantation of organs or haematopoietic (particularly allogeneic) cells.

Patients undergoing haematopoietic stem cell transplantation (HSCT) represent a population with a high risk of reactivation of HBV infection which may lead to life-threatening complications (fulminant hepatitis, fibrosing cholestatic hepatitis). The above applies in particular to patients after allogeneic HSCT (alloHSCT) who receive immunosuppressive therapy, with risk factors of reactivation including age > 50 years and graft-versus-host disease (GVHD) [12, 13]. Patients considered as eligible for HSCT as well as their donors should be subject to mandatory screening including tests for HBsAg, anti-HBs, anti-HBc and HBV-DNA before the transplantation procedure. This allows the identification of high-risk patients (positive for HBsAg and/or HBV-DNA and/or anti-HBc and/or anti-HBs where no information is available about vaccination), and high-risk donors (positive for HBV-DNA, HBsAg, anti-HBc, anti-HBs where no information is available about vaccination). Retrospective analyses show that the risk of reactivation applies to 40-60% of patients positive for HBsAg and/or anti-HBc before transplantation.

The choice of the management approach depends to a significant extent on the degree of risk of HBV reactivation associated with the type of applied therapy and its mechanism of action. For this reason, drugs used in immunosuppressive therapy, including biological and anticancer treatments, are classified as causing high, medium and low risk of HBV reactivation in patients with overt (HBsAg-positive) or occult (HBsAg-negative, anti-HBc-positive) HBV infection [14-16].

High risk (> 10%) of HBV reactivation is associated with:
- B-cell depleting drugs (rituximab, ofatumumab, ustekinumab, obinutuzumab, natalizumab, alemtuzumab, ibritumomab, tiuxetan),
- anthracyclines (doxorubicin, epirubicin),
- glucocorticosteroids used systemically in high doses (prednisone > 10 mg/kg daily for > 4 weeks),
- highly potent TNF-α inhibitors (infliximab, adalimumab, certolizumab, golimumab),
- transarterial chemoembolization (TACE) of the liver in the treatment of hepatocellular carcinoma.

Moderate risk (1-10%) of HBV reactivation in HBsAg-positive individuals is associated with:
- less potent TNF-α inhibitors (etanercept),
- cytokine inhibitors (abatacept, ustekinumab, mogamulizumab, natalizumab, vedolizumab),
- calcineurin inhibitors (cyclosporin, tacrolimus),
- tyrosine kinase inhibitors (imatinib, nilotinib),
- proteasome inhibitors (bortezomib),
- histone deacetylase inhibitors (romidepsin),
- glucocorticosteroids used systemically in moderate doses (prednisone < 10 mg/kg daily for < 4 weeks).

Low risk (< 1%) of HBV reactivation in HBsAg-positive individuals is associated with:
- antimetabolites (azathioprine, methotrexate, 6-mercaptopurine),

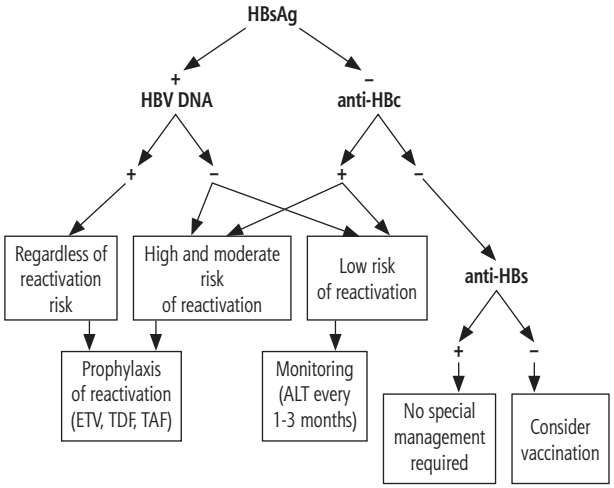


**Fig. 1.** Management depending on the risk of reactivation and serological and virological status

- glucocorticosteroids used in low systemic doses or topically.

The risk of reactivation in HBsAg-negative, anti-HBc-positive patients taking the above-mentioned drugs is usually lower, with the exception of drugs causing B-cell depletion, where it is as high as in HBsAg-positive patients.

## Prophylaxis

According to the recommendations, the prophylaxis of HBV reactivation and the treatment of HBV infection diagnosed during immunosuppression should be based on nucleoside or nucleotide analogues (NAs) with high potency. The group comprises entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF). Lamivudine and other NAs (adefovir, telbivudine) are not recommended because of their weaker antiviral activity and the risk of selection of resistant strains, but they may be used in situations where ETV, TDF or TAF are not feasible therapeutic options.

Entecavir has superior efficacy to lamivudine in preventing HBV reactivation. In a prospective study involving 121 DLBCL patients treated with the R-CHOP regimen (rituximab, cyclophosphamide, adriblastin, vincristine, prednisone), the prevalence of HBV reactivation, hepatitis and treatment discontinuation was significantly lower in patients treated with entecavir compared to lamivudine (6.6% vs. 30%, 0% vs. 13.3%, 1.6% vs. 18.3%, respectively) [17]. In the cross-sectional study conducted by Kim *et al*., the rate of HBV reactivation was significantly lower for entecavir as compared with lamivudine prophylaxis (6.3% vs. 39.3%) [18]. A metaanalysis of the clinical studies GOYA and GALLIUM found that prophylaxis was a factor reducing the risk of reactivation of HBV infection (10.8% vs. 2.1%) in HBsAg(–)/anti-HBc(+) patients, with the majority of patients receiving entecavir. In recent years, reports on the efficacy of tenofovir in the prophylaxis of reactivation of HBV infection have also been published. Buti *et al*. conducted a randomized phase IV clinical study demonstrating a significantly lower reactivation rate in HBsAg(–)/anti-HBs(+) patients with lymphoma treated with rituximab-based immunochemotherapy who received prophylaxis with tenofovir, as compared to preemptive treatment (0% vs. 10.7%, $p = 0.09$) [19].

A metaanalysis of existing studies comparing the efficacy of various drugs in the prophylaxis of HBV reactivation in patients undergoing haematopoietic cell transplantation has shown a lower event rate in patients receiving entecavir than lamivudine (1.9% vs. 11.5%, respectively). However, there are no data about the prophylaxis with telbivudine, adefovir and tenofovir in the group of patients with HSCT [12].

## Recommended management

All potential candidates for therapies increasing the risk of reactivation should be tested for HBsAg, anti-HBc-total, and anti-HBs, and patients with detectable HBsAg additionally for the presence of HBV-DNA (Fig. 1). The tests should be conducted before the initiation of immunosuppressive therapy, preferably immediately after the establishment of diagnosis which may result in the application of such therapy in the future. Further patient management depends on the results of the tests referred to above.

Patients without any of the above three serological markers of HBV infection should be considered for vaccination against hepatitis B. Preferably, vaccination should be administered before treatment, and if not possible, within 3 months after the completion of therapy, in the vaccination schedule of 0-1-6 months, or 0-1-2-12 months in urgent cases. In patients with oncohaematological disorders as well as other congenital and acquired immunodeficiencies above 20 years of age, the recommended procedure is to administer the vaccine at a higher dose (40 μg) in the 0-1-2-6 month vaccination schedule. It is advisable to evaluate the efficacy of vaccination 4 to 6 weeks after the final dose. The so-called accelerated vaccination schedule (1-7-21 days) has low efficacy, not exceeding 30%, so it is not recommended in patients with immune deficits.

- Patients with an established diagnosis of HBV infection receiving NAs should continue their therapy for as long as HBV-DNA is undetectable. Otherwise, a change of treatment should be considered on the

basis of current recommendations for the treatment of HBV infections [20].

- HBsAg-positive individuals with detectable HBV-DNA should receive NA prophylaxis regardless of the level of HBV reactivation risk. NAs should be started as early as possible before the introduction of immunosuppressive therapy which should optimally begin at HBV-DNA undetectability. However, achieving undetectable HBV-DNA levels cannot justify the deferment of immunosuppressive therapy. During immunosuppressive therapy, HBV-DNA should be monitored at intervals of not more than 3 months. NA prophylaxis should continue for the entire treatment period, and for at least 18 months after its completion. For another 12 months after the completion of prophylaxis of HBV reactivation, patients should be monitored by evaluating the concentration of HBV-DNA at intervals not exceeding 3 months.
- HBsAg-positive patients without detectable HBV-DNA, and HBsAg-negative/anti-HBc-positive patients scheduled for therapy with (a) drug(s) associated with a high or medium risk of reactivation should also begin the prophylaxis of HBV reactivation with NAs according to the principles set out above.
- In patients not requiring prophylaxis of HBV reactivation (HBsAg-positive individuals without detectable HBV-DNA, and HBsAg-negative/anti-HBc-positive patients treated with agents associated with a low risk of reactivation), ALT activity should be monitored every 1-3 months in the course of immunosuppressive therapy. Patients found to have increased ALT activity should be tested for the presence of HBV-DNA, and receive treatment with a fast-acting NA (ETV, TDF, TAF) on an urgent basis. If the HBV-DNA test results are expected to be available within a longer time frame, the introduction of NA treatment should be considered immediately after elevated ALT activity is detected.

Current international recommendations for patients treated by autologous or allogeneic HSCT are as follows [21].

- HBsAg-positive patients, regardless of their HBV viral load, should receive treatment with entecavir or lamivudine. Treatment should be started at least one week before the transplant procedure and continued for at least a year after the completion of immunosuppressive therapy. The duration of treatment should be established on a case-by-case basis, and it may even last indefinitely in patients after allo-HSCT.
- Anti-HBc-positive patients should receive antiviral prophylaxis for a period of at least 18 months after the end of immunosuppressive treatment. Prophylaxis should be continued until immune reconstitution (CD4+ > 200-400 cells/mm$^3$). Following the completion of prophylaxis, long-term monitoring of HBV viral load is recommended.
- Patients receiving allo-HSCT from anti-HBc-positive donors should receive long-term antiviral prophylaxis.
- Patients undergoing HSCT should be vaccinated against hepatitis B, and the concentration of anti-HBs antibodies should be monitored after the transplantation procedure. A recombinant vaccine is used from the sixth month after transplantation. Three doses are administered in the schedule of 0-1-2 months, and as required (anti-HBs titre < 10 IU/ml), followed by a booster dose of 20 μg or 40 μg administered 18 months post HSCT (12 months after the first dose) with a titre check after the administration of the fourth dose.
- Donor vaccination is recommended in HBV-positive recipients.

The duration of prophylaxis and antiviral treatment in post-HSCT patients is not clearly defined, as it depends on the use of immunosuppressants and on the quality of immune reconstitution, but should be longer than 12 months. The risk of selection of resistant viral strains during long-term prophylaxis with lamivudine is particularly high in this group (60%), so it appears that new-generation drugs should demonstrate greater efficacy. However, immune disturbances observed after allo-HSCT also contribute to reduced efficacy of new antiviral drugs in this group of patients: a decrease in the number of HBV-specific CD8+ cells, reduced production of interferon gamma, elevated concentration of interleukin 10, and an increase in the number of CD19+ cells [22].

## Paediatric aspects

In 1978-1996, the percentage of HBV-infected children with haematological and oncological diseases in Poland was 44.7% [23]. This translated into poorer outcomes of oncological treatment, and a greater number of both immediate and remote complications. In some patients, chemotherapy could not be continued because of hepatologic complications. The majority of paediatric haematooncology centres began to gradually introduce programmes of active and passive prophylaxis of HBV infections during intensive and maintenance chemotherapy. As a result, the rate of HBV infection in the paediatric population has been reduced to 7.1% [23, 24]. In the meantime, mandatory vaccinations began to be gradually introduced in neo-

nates and infants in Poland: in selected provinces from 1993, and throughout the country from 1996 onwards. Additionally, in 2000, a vaccination programme for 14-year-olds born in 1986 was launched.

The latest data (2012-2017) covering all paediatric treatment centres indicate that the prevalence of HBV infections in paediatric oncology and haematology departments is 0.02% (1/5,628), and in paediatric HSCT departments approximately 0.1% (1/971).

## Diagnostics and monitoring of HBV infections in children undergoing diagnosis and oncological treatment

All children in Poland diagnosed with cancer routinely undergo HBsAg tests. In addition, the concentration of anti-HBs antibodies is determined in a proportion of paediatric patients. Extended serological and/or molecular diagnostics of HBV is provided in patients with clinical or biochemical indications. Prior to the HSCT procedure, irrespectively of age, patients must be tested for HBV markers including HBs antigen, anti-HBs antibodies, total anti-HBc and HBV-DNA. Donors of hematopoietic cells are tested for HBsAg, anti-HBc (total and IgM), and HBV-DNA.

## Vaccinations in children with acute leukaemias undergoing chemotherapy

The latest European recommendations (ECIL7, *European Conference on Infections in Leukaemia*) for children with acute leukaemia recommend anti-HBV vaccination during induction and reinduction chemotherapy only in centres with a high risk of HBV transmission. At the same time, within 3-6 months after the end of maintenance chemotherapy, a booster dose of HBV vaccine is recommended in all children vaccinated during infancy, and a full vaccination course is advised in previously unvaccinated children, in line with national recommendations [25].

At the time of diagnosis of acute leukaemia, the need to start chemotherapy leads to temporary postponement of all protective vaccinations. During intensive chemotherapy, the prevention of HBV infections involves an institutional policy of patient isolation, application of the principles of disinfection, disposable equipment, immunoglobulins, and compliance with guidelines for the transfusion of blood products. Immunity and immunological memory developed as a result of previous vaccinations are also partially active.

In such situations, in children born from HBV-positive mothers, an accelerated vaccination schedule (20 μg of recombinant HBV vaccine on days 0-14-28 plus 1-2 additional vaccine doses) is recommended, providing efficacy in 23-35% of children [25].

The final and the longest phase of chemotherapy in children with acute leukaemias is maintenance treatment (up to 24 months from the onset of therapy). It is estimated that after its completion HBV seroconversion is maintained in only 46% of children, though immunological memory persists in over 80% of paediatric patients [25]. This allows initiating a revaccination programme within 3-6 months after the end of oncological treatment, particularly in children both with acute lymphoblastic and myeloblastic leukaemias.

## Recommendations

An accelerated vaccination schedule (3-5 doses), administered at the time of cancer diagnosis, is recommended in children at a high risk of HBV transmission. Additional administration of HBIG may increase the level of protection against HBV infection.

During a period of 3-6 months, patients with acute leukaemia who previously completed a full course of HBV vaccinations should receive a booster dose of HBV vaccine after finishing oncological treatment – regardless of the concentration of anti-HBs antibodies.

During a period of 3-6 months, patients with acute leukaemia who were not previously vaccinated against HBV should begin and complete a full course of HBV vaccinations after finishing oncological treatment, in line with national recommendations.

During a period of 3-6 months, patients with acute leukaemia who previously received an incomplete course of anti-HBV vaccinations should be given the missing doses of the HBV vaccine, without repeating the doses already administered, after finishing oncological treatment [25].

## Vaccinations in children undergoing haematopoietic cell transplantation

Current European recommendations (ECIL7) applicable to all HBV non-infected patients (also children), including individuals vaccinated against HBV, recommend a full course of HBV vaccinations over a period of 6-12 months post HSCT, in line with national recommendations [26].

Post-HSCT vaccinations against HBV serve a triple purpose: a) ensure patient protection following the loss of immunity from previous vaccinations due to HSCT in line with national recommendations; b) protect the patient from infection in cases involving anti-HBc-positive donors; c) reduce the risk of reverse seroconversion

in patients previously infected with HBV. Even though donors transfer their anti-HBV immunogenicity, and recipients are previously vaccinated against HBV, half of all patients lose their immunity within 6 months, and 90% within 5 years after HSCT [26].

The rate of seroconversion in patients vaccinated after HSCT is 64%, and it is lower in patients with chronic GVHD, but not in cases of T cell depletion used during the transplantation or rituximab treatment (for a period with a median of 16 months). There are no data concerning the value of an increased vaccine dose (40-80 μg) in post-HSCT patients.

Anti-HBc-positive donors (even if they are HBV-DNA-negative) may transmit HBV infection to recipients. In such situations, the recommended procedure is recipient vaccination prior to HCT: an accelerated vaccination course (days 0-10-21) producing a response in 70% of healthy people. In previously HBV-infected patients treated with antiviral drugs, an additional vaccination may have a protective effect against reverse seroconversion.

The concentration of anti-HBs antibodies should be determined after HCT and 1-2 months after the third vaccine dose. Non-responders (anti-HBs < 10 IU/l) can be considered for repetition of a complete vaccination cycle, however no data are available on the efficacy of this approach.

The Polish Society of Paediatric Oncology and Haematology recommends the initiation of HBV vaccinations in patients 6-12 months both after allo- and auto-HCT, concurrently with vaccinations against diphtheria (with an increased amount of the diphtheria antigen), tetanus, pertussis (acellular vaccine), meningococci and human papillomavirus (regardless of gender), in patients without GVHD symptoms. Patients should meet the following conditions: absolute lymphocyte count 750/μl, period of at least 6 months after the last dose of anti-CD20 therapy, without immunoglobulin substitution (not applicable to influenza vaccination). In addition, in patients after alloHSCT – without active chronic high-grade GVHD (even with dual immunosuppressive therapy) [27].

Vaccination against HBV should be administered to all patients over a period of 6-12 months, both after allo- and autoHSCT: 3 doses in patients with anti-HBs concentration < 10 IU/l or 1 dose if the concentration of anti-HBs > 10 IU/l (although ECIL does not recommend vaccination in this patient group) [27].

## Disclosure

Authors report no conflict of interest.

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